Hypophosphatemia
An Evidence-based Problem-Solving Approach to Clinical Cases

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Hypophosphatemia is defined as a serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L). Hypophosphatemia is caused by inadequate intake, decreased intestinal absorption, excessive urinary excretion, or a shift of phosphate from the extracellular to the intracellular compartments. Renal phosphate wasting can result from genetic or acquired renal disorders. Acquired renal phosphate wasting syndromes can result from vitamin D deficiency hyperparathyroidism, oncogenic osteomalecia, and Fanconi syndrome. Genetic disorders of renal hypophosphatemic disorders generally manifest in infancy and are usually transmitted as an X-linked hypophosphatemic rickets. Symptoms of hypophosphatemia are nonspecific and most patients are asymptomatic. Severe hypophosphatemia may cause skeletal muscle weakness, myocardial dysfunction, rhabdomyolysis, and altered mental status. The diagnostic approach to hypophosphatemia should begin with the measurement of fractional phosphate excretion; if greater than 15% in the presence of hypophosphatemia, the diagnosis of renal phosphate wasting is confirmed. Renal phosphate wasting can be divided into 3 types based upon serum calcium levels: primary hyperparathyroidism (high serum calcium level), secondary hyperparathyroidism (low serum calcium level), and primary renal phosphate wasting (normal serum calcium level). Phosphate supplementations are indicated in patients who are symptomatic or who have a renal tubular defect leading to chronic phosphate wasting. Oral phosphate supplements in combination with calcitriol are the mainstay of treatment. Parenteral phosphate supplementation is generally reserved for patient with life-threatening hypophosphatemia (serum phosphate < 2.0 mg/dL). Intravenous phosphate (0.16 mmol/kg) is administered at a rate of 1 mmol/h to 3 mmol/h until a level of 2 mg/dL is reached.

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INTRODUCTION

Phosphate is a predominately intracellular anion with a concentration of approximately100 mmol/L. The intracellular concentration of phosphate is 100 times greater than the plasma concentration. The average diet provides 800 mg to 1400 mg of phosphate daily. Of this, 70% is absorbed through the intestine, mainly by passive transport, but there is also some active transport, stimulated by vitamin D metabolites. Normal plasma level is between 2.8 mg/dL and 4.5 mg/dL. The main organ of regulation of phosphate is the kidney. Phosphate is filtered by the glomeruli and mostly reabsorbed (greater than 85%) in the proximal tubule

in a cotransport with sodium. This cotransport is regulated by serum phosphate level and parathyroid hormone (PTH). Parathyroid hormone inhibits the cotransport mechanism and increases urinary excretion of phosphate. Because the ionization of acid of phosphate is 6.8, at the normal serum pH of 7.4 the univalent species is 4 times as prevalent as the divalent species.[1,2]

Phosphate is involved in virtually every intracellular reaction and it is the body's source of chemical energy, adenosine triphosphate. Phosphate is also the main source of intracellular buffer and is involved in cascades within the coagulation and immune systems.[3,4]

HYPOPHOSPHATEMIA

Hypophosphatemia is defined as a serum phosphate level less than 2.5 mg/dL (0.8 mmol/L).[5] Hypophosphatemia is caused by inadequate intake, decreased intestinal absorption (malabsorption, phosphate binding antacids, and vitamin D deficiency),[4,6] excessive urinary excretion (hyperparathyroidism, vitamin D deficiency, oncogenic osteomalacia, and familial hypophosphatemic rickets),[7-13] or redistribution from extracellular into intracellular compartments (treatment of diabetic ketoacidosis, acute respiratory alkalosis, refeeding syndrome, and hungry bone syndrome).[14-17] Oncogenic osteomalacia is a paraneoplastic syndrome characterized by osteomalacia, hypophosphatemia, renal phosphate wasting, bone pain, and muscle weakness due to a circulating inhibitor of phosphate transport in the serum of patients with tumor-induced osteomalacia.[11,18] Familial hypophosphatemic rickets is the most common inherited form of rickets and is characterized by short stature, bone pain, radiographic evidence of rickets, renal phosphate wasting, and inappropriately low levels of serum concentration of 1,25-dihydroxyvitamin D. Familial hypophosphatemic rickets is usually transmitted as an X-linked dominant disorder (XHR), although the autosomal dominant hypophosphatemic rickets (ADHR) has also been described.[11,13]

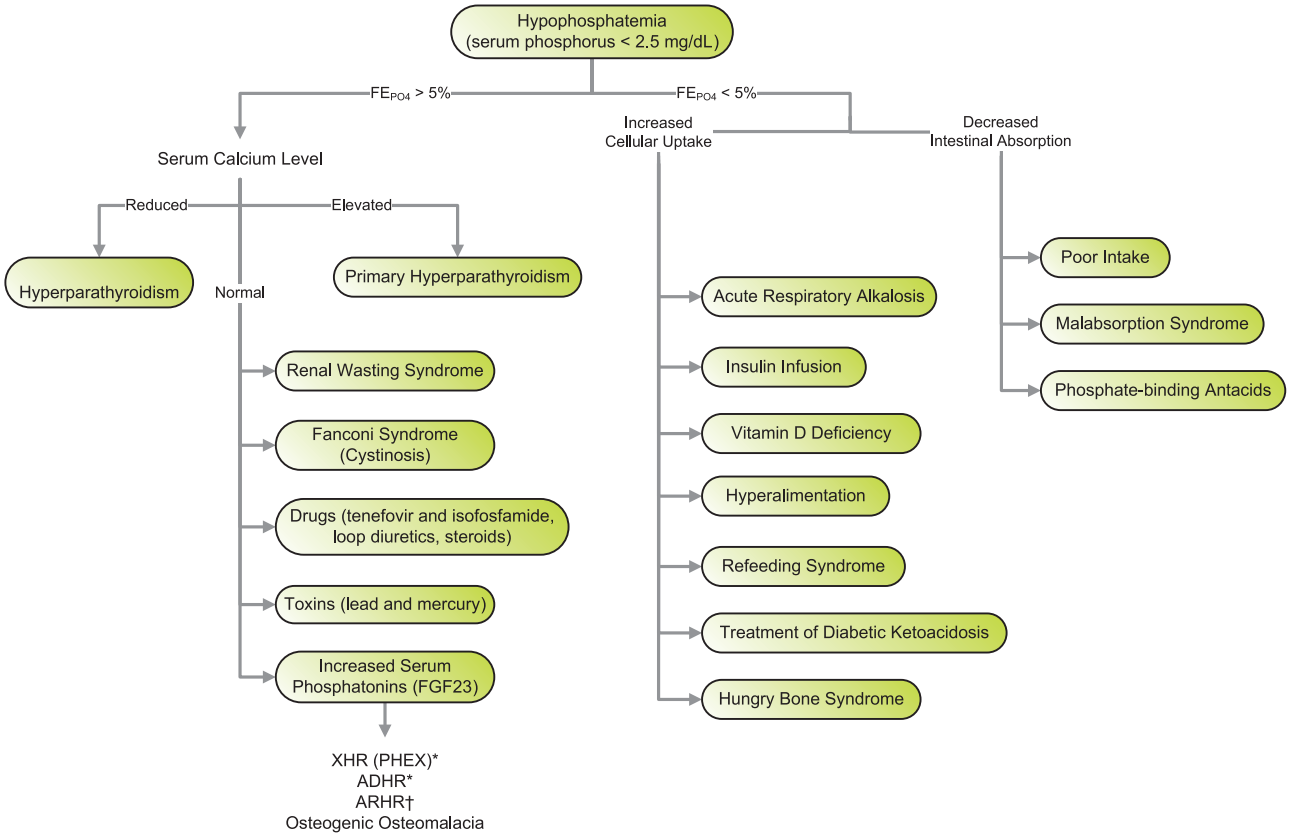
Mutations in the phosphate-regulating gene with homologies to endopeptidases (*PHEX*) and the fibroblast growth factor 23 (*FGF23*) are identified as the causes of XHR and ADHR disorders, respectively.[12,13] Autosomal recessive form of familial hypophosphatemic rickets (ARHR) associated with hypercalciuria is a rare genetic disorder that is caused by a mutation in the *SLC34C3* that encodes sodium-phosphate transporter.[19] There are two types of ARHR. In type 1, the defect is in renal 1-α-hydroxylation. Type 2 ARHR is characterized by end-organ resistance to the effects of 1,25- dihydroxyvitamin D. These patients, in contrast to patients with XHR or ADHR, have low plasma PTH and normal 1,25-dihydroxyvitamin D levels.[19,20]

Symptoms of hypophosphatemia are nonspecific and highly dependent on its cause, duration, and severity. Most patients with hypophosphatemia are asymptomatic. In general, patients may complain of skeletal muscle weakness,[21] particularly the respiratory muscle.[22] Severe hypophosphatemia may cause myocardial dysfunction, ventricular arrhythmias, rhabdomyolysis, and altered mental status.[23-25]

If the diagnosis of hypophosphatemia is not evident by history and physical examination, then measurement of urinary phosphate excretion should be helpful. Phosphate excretion can be measured either from a 24-hour urine collection or by calculation of the fractional excretion of filtered phosphate (FE_{PO4}) from a random urine specimen. The formula used to make the latter calculation is the same as that for fractional excretion of sodium:

FE_{PO4} = (urine phosphate × serum creatinine × 100)/(serum phosphate × urine creatinine)

The kidney is an important regulator of phosphate balance. Under normal physiologic condition, the FE_{PO4} varies between 5% and 20%. The FE_{PO4} should be less than 5% in the presence of low plasma phosphate concentration. When FE_{PO4} is greater than 5% in the presence of low plasma phosphate concentration, the cause of the hypophosphatemia is renal phosphate wasting.[9,10] Renal phosphate wasting can be divided into 3 types based upon the serum calcium level: primary hyperparathyroidism (high serum calcium level), secondary hyperparathyroidism (low serum calcium level), and primary renal phosphate wasting (normal serum calcium level). The differential diagnosis of hypophosphatemia with appropriate renal phosphate retention (FE_{PO4} less than 15%) includes increased cellular uptake and reduced net intestinal absorption (Figure).



Diagnostic approach to the patient with hypophosphatemia. FE_{PO4} indicates fractional phosphate excretion; FGF23, fibroblast growth factor 23; XHR, X-linked hypophosphatemic rickets; ADHR, autosomal dominant hypophosphtemic rickets; and ARHR, indicates autosomal recessive.

*Low serum 1,25-dihydroxyvitamin D level
†Hypercalciuria

TREATMENT

Therapy is highly dependent on the cause, severity, and duration of hypophosphatemia. The average patient requires 1 g to 2 g (32 mmol to 64 mmol) of phosphate per day to replenish the body stores.[6,26,27] Oral phosphate supplements in combination with calcitriol (15 ng/kg/d to 30 ng/kg/d) are also useful for the treatment of the genetic disorders of renal phosphate wasting and can often normalize phosphate levels and decrease bone pain.[28,29]

Parenteral phosphate supplementation is generally reserved for patients with life-threatening hypophosphatemia (serum phosphate level < 2.0 mg/dL).[30-32] Suggested rates of safe delivery of phosphate range from 1 mmol/h to 3 mmol/h. An easy-to-use weight-based regimen is to administer 0.08 mmol/kg to 0.16 mmol/kg (2.5 mg/kg to 5.0 mg/kg) over 6 hours, depending on the severity of the hypophosphatemia. Each milliliter of sodium or potassium phosphate solution contains 3 mmol of phosphate; this translates to 0.3 mol/h to 1.0 mol/h. The plasma phosphate concentration should be monitored every 6 hours and the patient switched to oral replacement until a level of 2 mg/dL is reached.

Vitamin D supplementation is indicated in patients with vitamin D deficiency. The recommended daily vitamin D intake is 400 IU to 800 IU. Patients with significant renal insufficiency benefit from oral 1,25-dihydroxyvitamin D supplements.[29] Patients with primary hyperparathyroidism benefit from parathyroidectomy. Patients with oncogenic osteomalacia are cured by excision of the tumor causing the renal phosphate wasting.[33]

CLINICAL QUIZ

The following clinical quiz was first published by the author in a book entitled *Clinical Decisions in Pediatric Nephrology: A Problem-Solving Approach*

to Clinical Cases,[7] and hereby is presented with some modification with the written permission of the publisher.

Case

A 30-month-old boy is evaluated for failure to thrive, muscle weakness, bone pain, and difficulty to walk over the last 10 months. The infant was born at term to a 28-year-old gravida 2, para 2 mother via vaginal delivery. The birth weight was 3.1 kg; length, 50 cm; and head circumference, 45 cm. The child's father had rickets as a child, which left severe deformities. He was taking vitamin D and phosphorous supplements. The patient's 6-year-old sister had a history of delayed gross motor milestones and frontal bossing. However, a workup never had been done, nor had the child been treated. A dietary history revealed that the child had been fed a soy-based formula since early infancy because he had been unable to tolerate cow's milk.

On examination, he appears as a thin male in no acute distress. Blood pressure is 96/51 mm Hg; pulse, 96 beats/min; respirations, 20/min; temperature, 37°C; weight, 11.3 kg (5th percentile); height, 80 cm (below 3rd percentile); and head circumference, 49 cm (50th percentile). Heart rate is regular and there are no extra sounds or murmurs. The lungs are clear. The abdomen is soft and there are no masses. The extremities are free of rashes or edema. Neurological examination shows moderate proximal-muscle weakness with lower extremity bowing. The rest of physical examination is uneventful. Laboratory studies reveal a hemoglobin level and a leukocyte count within reference ranges and a normal urinalysis. Serum sodium level is 137 mEq/L; potassium, 3.9 mEq/L; chloride, 100 mEq/L; bicarbonate, 28 mEq/L; blood urea nitrogen, 8 mg/dL; creatinine, 0.3 mg/dL; albumin, 4.2 g/dL; calcium, 10.2 mg/dL; phosphate, 1.9 mg/dL; magnesium, 1.7 mg/dL; and alkaline phosphatase, 1829 U/L (reference range, 50 U/L to 330 U/L). A random urine calcium-creatinine ratio is 0.18 (reference range, < 0.22 to 0.26).

Question 1. Which one of the following is most likely associated with his electrolyte abnormalities (select all that apply)?

(a). Muscle weakness
(b). Failure to thrive
(c). Bowing of the legs
(d). Bone pain
(e). Hyperthyroidism

The correct answers are *a*, *b*, *c*, and *d*. Muscle weakness, failure to thrive, radiographic evidence of rickets, and bone pain are classic clinical features of chronic hypophosphatemia.[21] Hypophosphatemia-induced muscle weakness involves skeletal muscle and may cause proximal myopathy, dysphasia, ileus, and even respiratory failure.[20,21]

Question 2. Which of the following studies should be done first in attempting to distinguish the diagnosis (select all that apply)?

(a). Fractional excretion of phosphate (FE_{PO4})
(b). Fractional excretion of calcium
(c). Arterial blood gases
(d). Plasma 25-hydroxyvitamin D level
(e). Plasma 1,25-dihydroxyvitamin D level

The correct answer is *a*. The first step in the diagnostic approach to hypophosphatemia is to establish whether hypophosphatemia is caused by inadequate dietary phosphate intake, reduced intestinal phosphate absorption, or excessive urinary losses of phosphate. This is done by evaluating the FE_{PO4}.[8,9]

In this patient, the random urine phosphate and creatinine excretion were 60 mg and 33 mg, respectively, and the FE_{PO4} was 28.6% (reference range, 10% to 15%).

Question 3. Which of one the following conditions should now be considered in the differential diagnosis (select all that apply)?

(a). Primary hyperparathyroidism
(b). Inadequate dietary intake
(c). Malabsorption of intestinal phosphate
(d). Ingestion of large quantities of phosphate binding antacids
(e). Vitamin D deficiency
(f). Fanconi syndrome
(g). X-linked hypphosphatemic rickets
(h). Oncogenic osteomalacia
(i). Hyperventilation

The correct answers are *e*, *f*, *g*, and *h*. The elevated FE_{PO4} signifies excessive urinary losses of phosphate. Renal phosphate wasting can result from genetic or acquired renal disorders. Acquired renal phosphate wasting syndromes can result from vitamin D deficiency, hyperparathyroidism, oncogenic osteomalecia, and Fanconi syndrome.[7,8,10,34] The genetic disorders of renal hypophosphatemic

disorders generally manifest in infancy and is usually transmitted as XHR.[11] The choice *a* is a wrong answer as serum calcium concentration is elevated in patients with primary hyperparathyroidism.[7] Answers to *b*, *c*, and *d* are also incorrect because of the inappropriately high FE_{PO4}. The choice *i* is a wrong answer because hyperventilation lowers serum phosphate level by promoting a shift of phosphate into the cells, leading to respiratory alkalosis and the FE_{PO4} is appropriately low.[14]

Additional laboratory studies revealed 25-hydroxyvitamin D was 71.8 ng/mL (reference range, 30 ng/mL to 100 ng/mL); 1,25-dihydroxyvitamin D, 15 pg/dL (reference range for children, 20 pg/dL to 70 pg/dL); and intact PTH, 44 pg/mL (4.6 pmol/L; reference range, 10 pg/mL to 68 pg/mL). There was no aminoaciduria or glucosuria. Radiographic studies revealed florid signs of rickets, including a rachitic rosary and cupping of the ribs, and fraying and flaying of the radius, ulna, femur, tibia, and fibula.

Question 4. What is the most likely diagnosis now (select all that apply)?

(a). Fanconi syndrome
(b). X-linked hypophosphatemic rickets
(c). Oncogenic osteomalacia
(d). Nutritional vitamin D deficiency

The correct answer is *b*. The condition appears to be genetic (strong family history of rickets) and the 1,25-dihydroxyvitamin D level is very low, consistent with this diagnosis.[11]

X-linked hypophosphatemic rickets is the most common inherited form of familial hypophosphatemic rickets and is characterized by growth retardation, defective bone mineralization, hypophosphtemia secondary to renal phosphate wasting, and inappropriately low serum concentration of 1,25-dihydroxyvitamin D. Patients with XHR have mutations in *PHEX*.[18,19] It has been postulated that *PHEX* plays a major role in the osteoblast cells differentiation and bone mineralization. It also increases renal phosphate reabsorption and promotes conversion of 25-hydroxyvitamin D to1,25-dihydroxyvitamin D through activation of 1-α-hydroxylase enzyme.[35,36] Answer *a* is incorrect because Fanconi syndrome is associated with generalized aminoaciduria and glucosuria. Answers *c* and *d* are not the correct answers, because of a strong family history of rickets.

Question 5. Which one of the following factor is most likely elevated in the plasma (select all that apply)?

(a). Parathyroid hormone-related protein
(b). Fibroblast growth factor 23
(d). Stannicalcin-1
(d). Calcitonin

The correct answer is *b*. Mutation in *PHEX* is associated with an increase in serum concentration of phosphatonins, including FGF23.[36] The mechanism by which this mutation leads to elevation in FGF23 is unknown. The elevated level of FGF23 inhibits renal and intestinal absorption of phosphate directly by inhibition of sodium-potassium-II cotransporters. It also inhibits activation of 25-hydroxyitamin D to 1,25-dihydroxyvitamin D through inhibition of 1-α-hydoxylase enzyme directly.[36] Autosomal dominant hypophosphatemic rickets has similar clinical manifestations, with hypophosphatemia, clinical rickets, and inappropriately low levels of 1,25-dihydroxyvitamin D. Genetic studies have identified mutation in *FGF23* as the cause of ADHR.[12]

The diagnosis of X-linked hypophosphatemic rickets was made based on the available laboratory data.

Question 6. What should be done next (select all that apply)?

(a). Treat with oral phosphate
(b). Treat with oral calcitriol
(c). Recommend total parathyroidectomy
(d). Order scintigraphy using octreotide labeled with indium-111

The correct answers are *a* and *b*. The goal of therapy is to improve growth, reduce the severity of bone disease, and minimize activity limitations. Phosphate supplements and calcitriol are the mainstays of therapy. Phosphorus administration lowers the level of ionized calcium in plasma and decreases calcitriol synthesis, leading to secondary hyperparathyroidism. Increased levels of PTH further aggravate urinary phosphate loss. Therefore, calcitriol administration is necessary to increase the intestinal absorption of calcium and phosphorus and to prevent secondary hyperparathyroidism. Therapy with calcitriol is initiated at 15 ng/kg/d to 20 ng/kg/d.[25,26] The dose is gradually increased over several weeks to 30 ng/kg/d to 60 ng/kg/d. Phosphate salts are given between 0.5 g/d to 4.0 g/d in divided doses every 4 hours. Healing

typically starts in 6 to 8 months after the start of therapy.[27,28]

The patient was treated with calcitriol and sodium phosphate, which led to significant improvement in the radiological signs of rickets after 6 months of therapy, and his serum phosphate level returned to normal.

Question 7. Which of the following acquired clinical disorders has similar clinical and biochemical findings as XHR and ADHR?

(a). Primary hyperparathyroidism
(b). Tumor-induced (oncogenic) osteomalacia
(c). Vitamin D deficiency
(d). Cystinosis

The correct answer is *b*. Oncogenic osteomalasia is a paraneoplastic syndrome characterized by osteomalacia, hypophosphatemia, renal phosphate wasting, bone pain, and muscle weakness. These patients usually have benign tumors of mesenchymal origin that produce phosphatonins, phosphaturic peptides.[32,37] Identification of the tumor can involve total body magnetic resonance imaging or scintigraphy using octreotide with indium-111 (since the tumors typically express somastatin receptors).[38] Patients with this syndrome require a combination of oral phosphate and calcitriol. This is because the use of phosphate alone may lower ionized calcium and lead to secondary hyperparathyroidism. Therapy should continue until the tumor can be identified and removed. Removal of the tumor leads to prompt reversal of the biochemical abnormalities and healing of the bone disease.[32] The vast majority of tumors are benign and do not recur. Prognosis is excellent for complete recovery.[32]

CONFLICT OF INTEREST

None declared.

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